Commentary by L. Lloyd Morgan, B.S. on "Use of mobile phones and cordless phones is associated with increased risk for glioma[1] and acoustic neuroma[2]" by Lennart Hardell, Michael Carlberg, Kjell Hansson Mild

Executive Summary

This review study provides comprehensive overview of virtually all studies which have examined the risk of brain tumors from wireless (cell and cordless) phone use. It also challenges industry's sound-bite, "With so many cellphones in use, if they are causing brain tumors, we should be seeing an increase incidence of brain tumors, but there is no increase," and the myriad studies that purported to prove that cellphones cannot possibly be causing brain tumors because there was not age-adjusted brain tumor incidence[3] increases.

The abstract states, "It is concluded that one should be careful using incidence data to dismiss results in analytical epidemiology." Industry's sound-bite is now being refuted by actual incidence data. This study cites Denmark and Australia as reporting about a doubling of glioblastoma multiforme, and we include in this Commentary USA age-specific incidence increased trends, 1990-2009, for <50 year olds with annual percentage increases as large as 3.4% per year. Perhaps such increases indicate the front-edge of a brain cancer tsunami?

To give a sense of just how comprehensive this review is here are the specific topics included in the Results portion of the paper:

- Brain tumours overall
- Glioma & Meta-analysis glioma
- Meningioma & Meta-analysis meningioma
- Acoustic neuroma & Meta-analysis
- Other types of brain tumours
- Risk to children and adolescents
- Danish cohort study on mobile phone users
- Hazard ratio (HR) for survival of patients with glioma
- Brain tumour incidence

[1] Brain cancer
[2] A tumor of the acoustic nerve
[3] Age-adjusted incidence is the incidence for the whole population adjusted by age (since most cancers are diagnosed in the elderly it tends to hide increases in specific groups).

The combination of multiple factors reviewed in this paper allows us to move from an initial view that brain tumors are *associated* with wireless (cell and cordless) phone use to a view that the overall evidence indicates there is *a causative link* between wireless phone use and brain tumors. The brain tumor risk factors are:

1. Ipsilateral use (tumor on same side as where wireless phone was used) finds the highest risk;
2. Cumulative hours of use finds the highest risk;
3. Years since first use finds the highest risk;
4. Regions of the brain which absorb the highest amount of wireless phone radiation (e.g., temporal lobe) have the highest risk);
5. Wireless first use of adolescents and children (<20 year olds) have the highest risk;
6. Rural cellphone users have higher risk that urban use;[4]

The discussion on hazard ratios provides a seventh factor which adds *additional evidence of a causative link*. Hazard ratio measures the risk of brain tumor death from cellphone use. This study reports,

> "Hazard ratio (HR) for survival was close to unity for all glioma cases for use of wireless phones, HR = 1.1, 95% CI = 0.9–1.2. However, latency >10 years increased HR to 1.2, 95% CI = 1.002–1.5. Increased ratio was found for both mobile phone use, HR = 1.3, 95% CI = 1.0005–1.6, and cordless phone use, HR = 1.3, 95% CI = 0.9–1.9. HR increased also with cumulative number of hours of use of mobile phone and cordless phone with statistically significant trend for tertiles (p = 0.01) of use of both phone types."

7. Risk of brain tumor death increases with cumulative hours of wireless phone use.

Since 2001 there have been 7 studies published which used a list of 1982-1995 Danish cellphone subscribers as a surrogate for cellphone use. It then compared this list of Danish citizens against all Danish citizens to determine the risk of cancers and neurological diseases. These studies are collectively known as the Danish Cellphone Subscriber Cohort "study." This review provides a very thorough analysis why this industry-funded "study" is so fraught with errors that it cannot be considered evidence of any kind. Indeed, where this study commonly states that it found no risk of brain tumors and many other disease, their actual data reports *statistically significant protection* from these diseases. This "protection" is an artifact of the highly flawed study design.

[4] Rural cellphones, controlled by the cell tower (AKA base station) typically radiate higher power than urban cellphones because rural cellphones are typically farther from a cell tower than are urban cellphones.

The critique of the Brain tumour Incidence section (3.12) is particular good. Of particular import given industry's campaign that no brain tumor incidence increase proves that cellphone are not causing brain tumors, it in the following paragraph:

> "In Denmark a statistically significant increase in incidence rate per year for brain and central nervous system tumours (combined) was seen during 2000–2009; in men +2.7%, 95% CI = +1.1 to 4.3% and in women +2.9%, 95% CI = +0.7 to 5.2% (http://www-dep.iarc.fr/NORDCAN/english/frame.asp). Updated results for brain and central nervous system tumours have been released in Denmark. The age-standardised [called "age-specific" in the USA] incidence of brain and central nervous system tumours increased with 40% among men and 29% among women during 2001–2010 (http://www.sst.dk/publ/Publ2011/DAF/Cancer/Cancerregisteret2010.pdf). A more recent news release based on the Danish Cancer Register stated that during the last 10 years there has been an increasing number of cases with the most malignant glioma type, glioblastoma multiforme (astrocytoma WHO grade IV), especially among men (http://www.cancer.dk/Nyheder/nyhedsartikler/2012kv4/Kraftig+stigning+i+hjern-esvulster.htm). So far these incidence data are not generally available."

They report in Australia for years between 2000 and 2008,

> "Adults aged ≥65 years recorded the largest proportion of malignant brain tumours, 52%. The Annual Percentage Change (APC) for malignant tumours increased statistically significant +3.9%, 95% CI +2.4 to 5.4%."

Not reported in this review was a poster presented at the American Public Health Association's meeting (October 2012), which reported annual percentage change (APC) of brain cancer incidence diagnosed between 1990-2009 increased by as high as 3.4% per year for ages <50 years old (see Appendix and Summary below).

In summary, Australia, Denmark, and the USA are reporting statistically significant annual increases in brain cancer rates:

Australia: 2000-2008, the most deadly brain cancer, glioblastoma multiforme (median survival <1 year), is significantly increasing in men and women at 3.9% per year!

Denmark: 2000-2009, male and female brain tumors are significantly increasing by 2.7% and 2.9% per year!

USA: 1990-2009, both male and female age-specific brain cancer incidence is increasing annually for ages less than 50 years; It is increasing significantly by

2.2% in males <20 years of age; 3.0% per year in women aged 20-29 and 3.4% per year in men aged 30-39![5]

The Discussion section states,

> "Certainly the methods used in Interphone may introduce selection bias. Patient lists are usually selective to use for drawing of controls and do not represent the whole population which is the source of the cases. Also random digit dialing has the potential to introduce selection bias since persons that are registered to subscribe a phone are usually wealthier than non-subscribers. Furthermore, it seems not to be the most appropriate method for selection of controls in a study on mobile phone use, and certainly not regarding cordless phones, since phone subscribers are selected as controls. Furthermore, later selection of controls from a pool with individual matching may give the possibility for selection bias if this is not done in a blinded manner as to exposure status."

While all of this is true, the Interphone study admitted that selection bias alone resulted in an underestimation of brain tumor risk by 10% but went further to admit that the overall underestimation was

> "...non-participation [selection] bias may have led to a reduction in the ORs for regular use of 5–15%, which is less than the observed reductions below the null in the ORs in ever regular mobile phone users for meningioma (21%, 95% CI 32–9) and glioma (19%, 95% CI 30–6; Table 2)."

Among the *unstated* underestimation risk factors was the Interphone's restricted age range (30-59 years), and perhaps the single largest underestimation risk factor, the *treatment of cordless phone use as a non-exposure*. The admitted and quite large underestimation of risk allows us to make sense of the seemingly incomprehensible statistically significant findings of *protection*s from short-term cellphone use in the Interphone study. The *protection is an artifact* of the admitted large underestimation of risk. Further it is reasonable to assume that the meningioma and glioma risks published by the Interphone Study Group should be increased by at least 21% and 19% respectively for all Odds Ratios (ORs) published in the Interphone study. This would typically change the statistically significant protection finding to non-significant results, and would increase many of the published non-significant increased risk to significant risks.

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[5] This was the same SEER database used by Little et al.

Appendix

Time Trends in Malignant Brain Tumors in the United States: SEER 1975-2009

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Objective: This study evaluates recent time trends in sex- and age-specific incidence of all malignant brain tumors by primary sites and histological subtypes in the US in order to generate hypotheses about possible explanations of these patterns.

Methods: SEER 9 Registry incidence data were retrieved by using SEER*Stat software (version 7.0.5) to obtain age, sex, year, and histologic-specific incidence rates between year of 1975 and 2009. Primary cancer sites and histologic subtypes of malignant brain tumors were identified based on ICD-O-3. Annual percent change (APC) of sex-specific brain tumor incidence by primary site was estimated by joinpoint regression, which was also used to estimate sex- and age-specific trends by histologic subtypes of brain tumors.

Results: Between 1975 and 2009, age-adjusted incidence rates for all malignant brain tumor increased in men until about 1987, decreasing thereafter; for black women incidence increased significantly between 1975 and 2008 (APC=0.72%, p=0.02, Figure 1). Malignant brain tumor incidence of frontal lobe, temporal lobe and brain stem significantly increased ($p<0.001$) for both men and women with larger increases for men than women (Table 1). From 1990-2009 for males and females <20, glioma incidence increased significantly (2.2% and 1.7% APC respectively) with similar patterns for men and women ages 20-29 (1.7 and 1.1 %), 30-39 years (3.4 and 3.0%) (Figure 2). During the same years non-significant

increased incidence occurred for combined temporal lobe, cerebellum, and frontal lobe only in women but was significant in both genders for ages 60+ (Figure 3).

Figure 1. Age-adjusted Incidence for all malignant brain tumors by race and sex, SEER 1975-2009

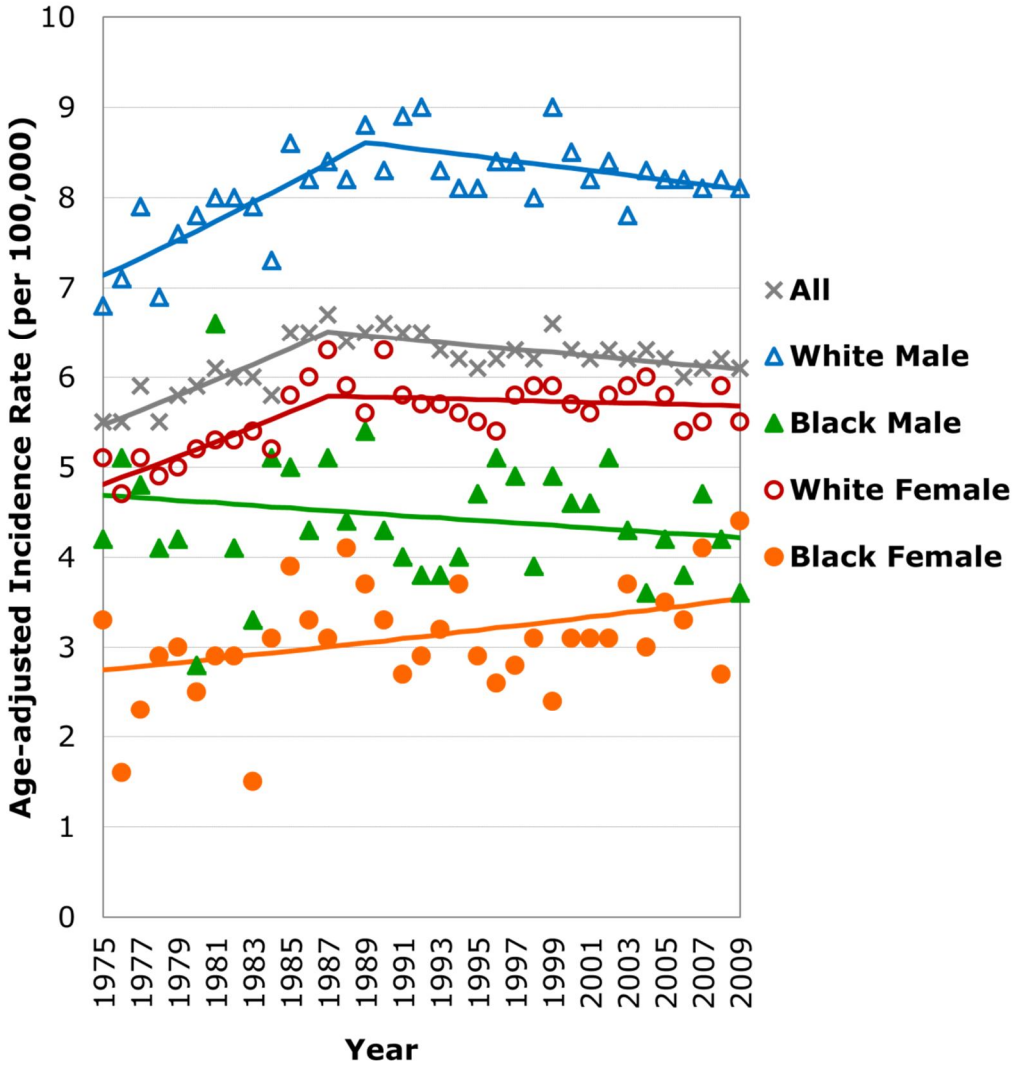


Table 1. Age-adjusted incidence of malignant brain tumors (per 100,000) by primary site, year, and sex

			Year							APC* (%)	P-trend
Primary Site	ICD-10	Sex	1975-79	1980-84	1985-89	1990-94	1995-99	2000-04	2005-09	1975-2009	
All brain	C71	M	6.94	7.41	8.35	8.94	8.47	7.94	7.78	0.22	0.120
		F	4.72	4.99	5.68	5.57	5.48	5.21	5.49	0.36	<0.001
Cerebrum	C71.0	M	0.42	0.49	0.52	0.56	0.45	0.40	0.40	-0.84	0.026
		F	0.31	0.32	0.36	0.33	0.30	0.32	0.30	-0.14	0.634
Frontal lobe	C71.1	M	1.35	1.46	1.62	1.71	1.72	1.85	1.20	1.18	<0.001
		F	1.07	1.05	1.29	1.14	1.28	1.31	1.54	1.13	<0.001
Temporal lobe	C71.2	M	1.15	1.16	1.45	1.63	1.57	1.48	1.56	0.89	<0.001
		F	0.68	0.66	0.88	0.86	0.83	0.95	0.93	1.06	<0.001
Parietal lobe	C71.3	M	0.99	1.08	1.16	1.11	1.05	1.00	0.96	-0.33	0.128
		F	0.63	0.70	0.82	0.77	0.64	0.65	0.64	-0.37	0.126
Occipital lobe	C71.4	M	0.17	0.26	0.27	0.29	0.29	0.27	0.24	0.36	0.379
		F	0.10	0.13	0.16	0.14	0.15	0.16	0.17	1.37	0.008
Ventricle, NOS	C71.5	M	0.12	0.12	0.18	0.15	0.13	0.15	0.12	0.01	0.987
		F	0.09	0.10	0.10	0.11	0.10	0.08	0.09	-0.44	0.434
Cerebellum, NOS	C71.6	M	0.40	0.39	0.45	0.48	0.40	0.44	0.35	-0.25	0.395
		F	0.31	0.28	0.31	0.29	0.35	0.34	0.32	0.39	0.170
Brain stem	C71.7	M	0.22	0.22	0.33	0.37	0.31	0.33	0.30	0.83	0.053
		F	0.15	0.19	0.27	0.30	0.27	0.28	0.29	1.56	<0.001
Overlapping lesion of brain	C71.8	M	1.20	1.46	1.51	1.49	1.45	1.21	0.99	-0.86	0.004
		F	0.72	1.02	0.95	1.01	0.94	0.78	0.60	-0.96	0.008
Brain, NOS	C71.9	M	0.93	0.76	0.85	1.16	1.11	0.82	0.88	-0.05	0.885
		F	0.66	0.54	0.55	0.62	0.62	0.64	0.61	0.06	0.854
Cerebral meninges	C70.0	M	0.13	0.14	0.12	0.13	0.09	0.12	0.09	-1.07	0.011
		F	0.08	0.14	0.12	0.14	0.13	0.11	0.09	-0.31	0.504

Figure 2. Annual percent change (%) of incidence rate in glioma by sex and age, SEER 1990-2009

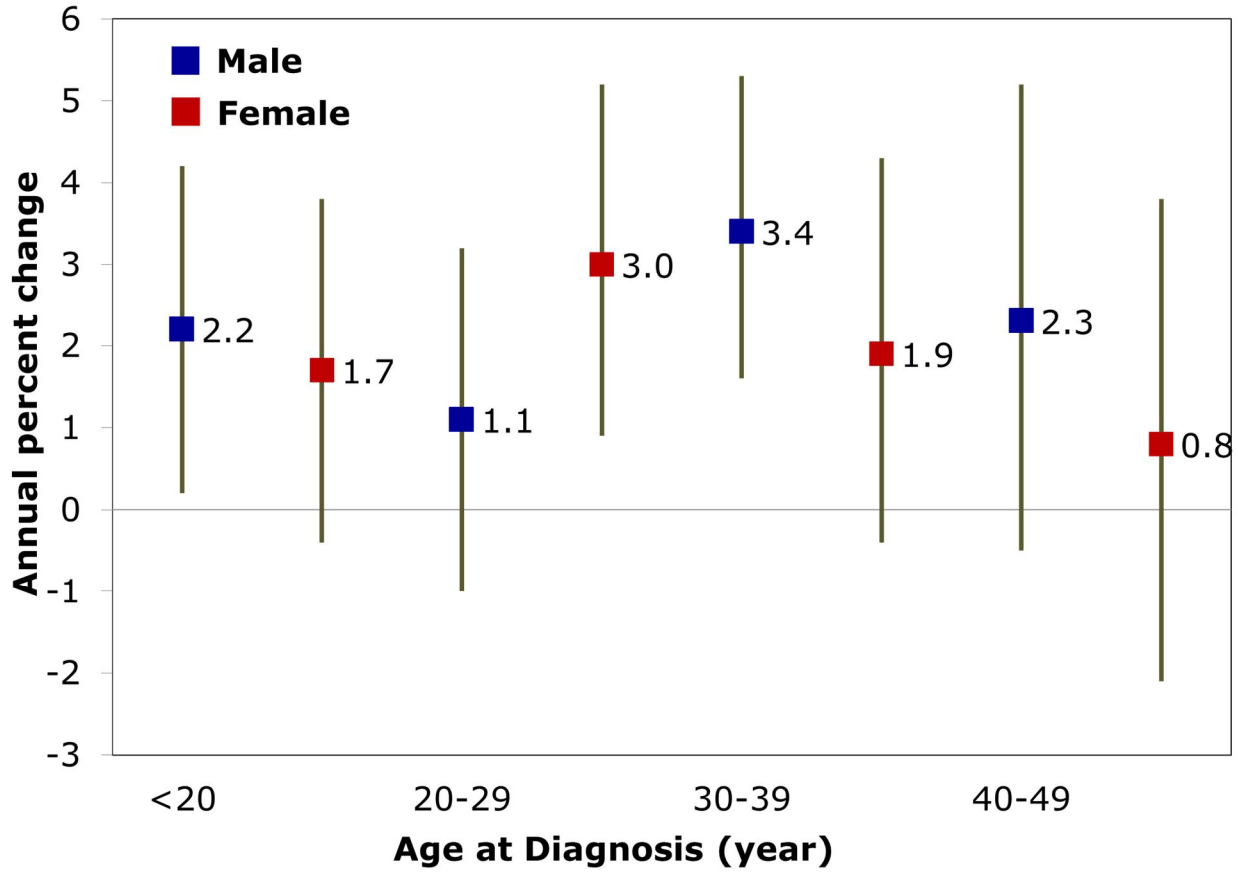
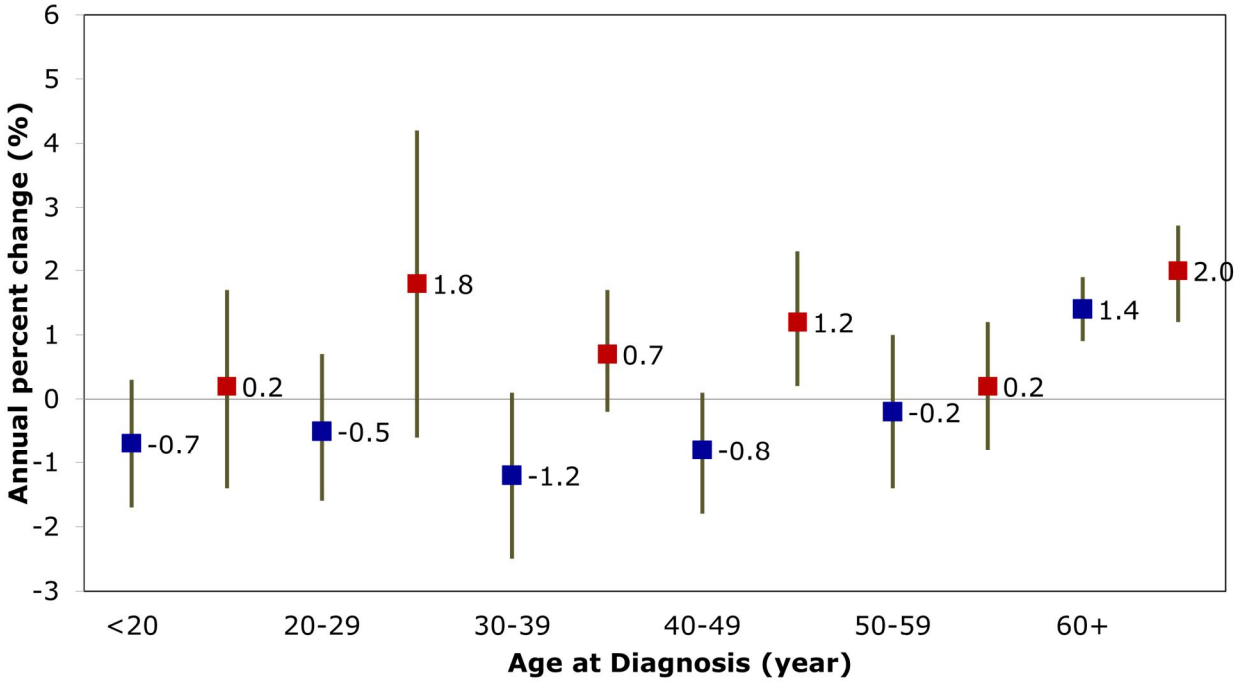


Figure 3. Annual percent change (%) of incidence rate in temporal lobe, cerebellum, and frontal lobe by sex and age, SEER 1990-2009



Conclusion: These increased rates for glioma in persons <50 years of age cannot be fully explained by diagnostic improvement and may reflect changes in some environmental risk factors, although the former are likely to play some role in increases in those over 60. Among the hypotheses that may be relevant are the increased use of diagnostic radiation, the growing use of cellphones in children and young adults, or other risk factors that are still to be discovered. Depending on cellphone frequencies between 81% to 86% of the cellphone radiation absorbed in the regions of the brain found in Figure 3, the consistent increases in women seen in Figure 3 suggests that women may either be at greater risk from cellphone radiation than men and/or have greater exposures to these and other neuro-oncogens.